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February 28, 2007  
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Travis M. Wohlers

**PATENT**  
**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

*In re* Application of:

Andrew Ellington

Serial No.: 09/776,252

Filed: February 2, 2001

For: SIGNALING APTAMERS THAT  
TRANSDUCE MOLECULAR  
RECOGNITION TO A DIFFERENTIAL  
SIGNAL

Group Art Unit: 1634

Examiner: B.J. Forman

Atty. Dkt. No.: CLFR:200US

Confirmation No.: 9740

**APPEAL BRIEF**

**MAIL STOP APPEAL BRIEF - PATENTS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313

Dear Sir:

Appellant submits this Appeal Brief to the Board of Patent Appeals and Interferences in response to the final Office Action dated August 17, 2006. Appellant filed a Notice of Appeal and a pre-appeal brief request for review on November 17, 2006. The Notice of Panel Decision from Pre-Appeal Brief Review was mailed December 29, 2006. Accordingly, the deadline for filing the Appeal Brief was January 29, 2007. A request for a one-month extension of time is included along with the required fee. The one-month extension brings the deadline for filing the Appeal Brief to February 28, 2007. The fee for filing this Appeal Brief is also included. Should any additional fees be required under 37 C.F.R. §§ 1.16 to 1.21, please consider this paragraph such a request and authorization to withdraw the appropriate fee from Fulbright & Jaworski L.L.P. Account No.: 50-1212/CLFR:200US.

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## **I. REAL PARTY IN INTEREST**

The real party in interest is the assignee, Research Development Foundation.

## **II. RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences.

## **III. STATUS OF THE CLAIMS**

Claims 1-28 have been canceled. Claims 29-43 are currently pending in the application.

A copy of the pending claims is provided in the Claims Appendix. Claims 29-43 stand rejected.

Appellant appeals the rejection of claims 29-43.

## **IV. STATUS OF AMENDMENTS**

No amendments are pending.

## **V. SUMMARY OF CLAIMED SUBJECT MATTER**

Independent claim 29 is directed to a method of transducing a conformational change in a signaling aptamer upon binding a ligand to an optical signal, the method comprising: (a) providing a signaling aptamer comprising a reporter molecule covalently coupled to an aptamer, wherein in an unbound state an optical signal produced by the reporter molecule is quenched by the aptamer's conformation and not by means of a separate quenching molecule covalently coupled to the signaling aptamer, relative to the optical signal produced by the reporter molecule when the aptamer undergoes a conformational change upon binding to its ligand; (b) contacting the signaling aptamer with the ligand under conditions whereby the signaling aptamer binds the ligand; and (c) detecting the optical signal produced by the reporter molecule as a result of the conformational change to the signaling aptamer upon binding the ligand. Specification, p. 6, ln. 16 to p. 7, ln. 14; p 17, ln. 1 to p. 18, ln. 10; p. 20, ln. 13 to p. 22, ln. 8; and FIGs. 2A and 2B).

## **VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

Claims 29-43 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claims 29-37 and 40-43 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Gold *et al.* (U.S. Patent No. 6,242,246) as defined by Pitner *et al.* (U.S. Patent No. 5,650,275).

Claims 29-34, 36-37, and 41 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Royer *et al.* (U.S. Patent No. 5,445,935).

Claims 38-39 stand rejected under §103(a) as being obvious over Gold as defined by Pitner (U.S. Patent No. 5,650,275) in view of Szostak (U.S. Patent No. 5,631,146).

## **VII. ARGUMENT**

### **A. Substantial Evidence is Required to Uphold the Examiner's Position**

Findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(A), (E), 1994. *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). Moreover, the Federal Circuit has held that findings of fact by the Board of Patent Appeals and Interferences must be supported by “substantial evidence” within the record. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). In *In re Gartside*, the Federal Circuit stated that “the ‘substantial evidence’ standard asks whether a reasonable fact finder could have arrived at the agency’s decision.” *Id.* at 1312.

Accordingly, it necessarily follows that an Examiner’s position on Appeal must be supported by “substantial evidence” within the record in order to be upheld by the Board of Patent Appeals and Interferences.

## B. The Claims Are Supported by Adequate Written Description

The examiner rejects claims 29-43 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the examiner asserts that the phrase “not by means of a separate quenching molecule covalently coupled to the signaling aptamer” in claim 29 introduces new matter. Appellant traverses this rejection.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). The disclosure in the present specification would convey to a person of ordinary skill in the art that the optical signal produced by the reporter molecule covalently attached to the signaling aptamer is quenched by the aptamer’s conformation and not by means of a separate quenching molecule covalently coupled to the signaling aptamer.

A “signaling aptamer” is an aptamer with a reporter molecule appended in such a way that upon conformational changes resulting from the aptamer’s interaction with a ligand, the reporter molecules yield a differential signal. The working examples provided in the present specification demonstrated that a ligand-dependent differential optical signal can be produced by a signaling aptamer in which a single reporter molecule has been covalently appended. For example, the signaling aptamer ATP-R-Ac13 has a single acridine moiety introduced in the place of the adenosine at position 13 of the aptamer (*see p. 21, ln. 16-18, and FIG. 2A*). The signaling aptamer DFL7-8 has a single fluoresceine molecule inserted between residues 7 and 8 of the aptamer (*see p. 21, ln. 18 to p. 22, ln. 2, and FIG. 2B*). As evident from the description of these aptamers, quencher molecules were not incorporated into their sequences (*see e.g., p 17, ln. 1 to*

p. 18, ln. 10; p. 20, ln. 13 to p. 22, ln. 8; and FIGs. 2A and 2B). The ATP-R-Ac13 and DFL7-8 aptamers showed marked increases in fluorescence intensity in the presence of their ligand (p. 22, ln. 6-8). Thus, the signaling aptamers of the presently claimed invention do not have a separate quencher molecule appended to the aptamer to mediate the optical signal produced by the reporter molecule.

The examiner has not identified any passages in the present specification that indicate that the signaling aptamers contain separate, covalently coupled quenching molecules. In fact, the examiner acknowledges that the ATP-R-Ac13 and DFL7-8 aptamers are not described as having quenching molecules (Action, p. 3). Moreover, the examiner states that “[w]hile the two aptamers provided in the specification are not described as having a quenching molecule, the aptamers function as quenchers.” (Action, p. 3). Thus, it appears that the examiner understands the specification to disclose that the optical signal produced by the reporter molecule is quenched by the aptamer’s conformation and not by means of a separate quenching molecule covalently coupled to the signaling aptamer. This indicates that a person skilled in the art would recognize in Appellant’s disclosure a description of the invention defined in the claims.

It appears that the examiner is rejecting the claims because there is no *in haec verba* recitation of the phrase “not by means of a separate quenching molecule covalently coupled to the signaling aptamer.” This position is legally unsupported, as there is no *in haec verba* requirement for written description. *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ 2d 1227, 1232 (Fed. Cir. 2000). For example, in *Ex Parte Parks*, the examiner rejected the claims on the grounds that there was no literal basis for the claim limitation “in the absence of a catalyst.” *Ex Parte Parks*, 30 U.S.P.Q.2D (BNA) 1234 (BPAI 1993). The Board reversed the examiner’s rejection noting that “Throughout the discussion

which would seem to cry out for a catalyst if one were used, no mention is made of a catalyst."

*Id.* Likewise, throughout the present specification, which would seem to "cry out" for a discussion of a separate quenching molecule covalently coupled to the signaling aptamer if one were used, there is no mention of such a quenching molecule. For example, in addition to the working examples discussed above, the present specification provides the following descriptions of a method of transducing a conformational change in a signaling aptamer upon binding a ligand to an optical signal (the paragraph numbers are according to the numbering in Publication No. US 2001/0046674):

**[0012]** In one embodiment of the present invention there is provided a method of transducing the conformational change of a signaling aptamer upon binding a ligand to a differential signal generated by a reporter molecule comprising the steps of contacting the signaling aptamer with the ligand wherein the signaling aptamer binds the ligand; and detecting the differential signal generated by the reporter molecule resulting from the conformational change of the signaling aptamer upon binding the ligand thereby transducing the conformational change.

**[0013]** In another embodiment of the present invention there is provided a method of transducing the conformational change of a signaling aptamer upon binding a ligand to an optical signal generated by a fluorescent dye. This method comprises the steps of contacting the signaling aptamer with the ligand wherein the signaling aptamer binds the ligand; and detecting the optical signal generated by the fluorescent dye resulting from the conformational change of the signaling aptamer upon binding the ligand thereby transducing the conformational change.

Neither of these passages (nor any other passages in the specification) mention a separate quenching molecule covalently coupled to the signaling aptamer.

In determining whether a claim satisfies the written description requirement, the question is whether the specification conveys to the those skilled in the art that, as of the filing date, the applicant was in possession of the claimed invention (MPEP § 2163.02). Furthermore, “[t]he written description requirement does not require the applicant ‘to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.’” *Union Oil Co. of California*, 208 F.3d at 997. As described in the preceding paragraphs, those of skill in the art would understand that Applicant was in possession, at the time the application was filed, of a method in which the optical signal produced by the reporter molecule covalently attached to the signaling aptamer is quenched by the aptamer’s conformation and not by means of a separate quenching molecule covalently coupled to the signaling aptamer. Appellant, therefore, respectfully requests that the Board overturn this rejection.

#### C. The Rejection Under 35 U.S.C. §102(e) Over Gold *et al.*

Claims 29-37 and 40-43 were rejected under § 102(e) as being anticipated by Gold *et al* (U.S. Patent No. 6,242,246). Appellant respectfully traverses this rejection.

Gold does not teach a method that comprises providing a signaling aptamer comprising a reporter molecule covalently coupled to an aptamer, wherein in an unbound state an optical signal produced by the reporter molecule *is quenched by the aptamer’s conformation and not by means of a separate quenching molecule covalently coupled to the signaling aptamer*, relative to the optical signal produced by the reporter molecule when the aptamer undergoes a

conformational change upon binding to its ligand. Rather, Gold discloses a method for quenching a fluorescent molecule using a fluorescent molecule and a separate quenching molecule covalently coupled to the signaling aptamer. Gold refers to the fluorescent molecule and the quencher molecule as “an energy transfer pair” (Col. 13, ln. 41-42; FIG. 5). An example of an energy transfer pair is fluorescein and tetramethylrhodamine (Col. 11, ln. 54-57). As illustrated in FIG. 5 of Gold (reproduced below), which the Action specifically cited to in support of its §102(e) rejection, fluorescence is quenched by a quenching molecule (52) in close proximity to the fluorescence molecule (53).

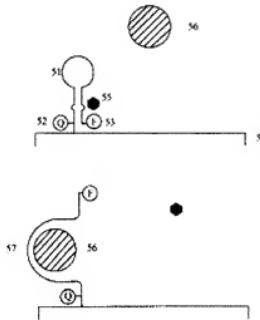


Fig. 5

In contrast, FIGs. 2A and 2B of the present specification disclose a fluorescence molecule (F) *with no separate quenching molecule covalently coupled to the signaling aptamer*, the absence of which represents an advance over the cited art. An advantage of Appellant's method is that it obviates the need for a quenching molecule to be engineered onto the aptamer.

Because Gold teaches a method whereby the fluorescence molecule is quenched by a quenching molecule rather than by the conformational change itself, Gold does not teach every element of Claim 29. Gold therefore does not anticipate independent Claim 29 or dependent Claims 30-37 and 40-43 under §102(e). Appellant, therefore, respectfully requests that the Board overturn this rejection.

**D. The Rejection Under 35 U.S.C. §102(b) Over Royer *et al.***

The Action rejects claims 29-34, 36-37, and 41 under § 102(b) as being anticipated by Royer (U.S. Patent 5,445,935). Appellant traverses this rejection.

The examiner failed to establish a *prima facie* case of anticipation. Royer does not teach a method that comprises providing a signaling aptamer comprising a reporter molecule covalently coupled to an aptamer, wherein in an unbound state an optical signal produced by the reporter molecule *is quenched by the aptamer's conformation and not by means of a separate quenching molecule covalently coupled to the signaling aptamer*, relative to the optical signal produced by the reporter molecule when the aptamer undergoes a conformational change upon binding to its ligand. Rather, Royer discloses a method of detecting a target compound in a sample by measuring the polarization of a fluorescently labeled molecule (*see e.g.*, Royer, col. 4, ln. 10-47). Polarization values depend upon solvent diffusion and tumbling motion of the fluorescent molecule (*see Royer, col. 4, ln. 21-28*). When a fluorescently labeled molecule binds with the target compound, its size is effectively increased and the tumbling slows, which changes the polarization (*see Royer, col. 4, ln. 21-28*). Thus, according to Royer's method, the target compound is detected by a change in polarization value which is the result of the slowing of the fluorescently labeled molecule's tumbling speed. In contrast, according to the methods of the present invention the change in the optical signal is the result of a conformational change to the

signaling aptamer. Accordingly, Royer does not teach every element of the current claims. Appellant, therefore, respectfully requests that the Board overturn this rejection.

**E. The Rejection Under 35 U.S.C. §103(a) Over Gold *et al.* as Defined by Pitner *et al.* in View of Szostak *et al.***

Claims 38-39 were rejected under §103(a) as being obvious over Gold as defined by Pitner (U.S. Patent No. 5,650,275) in view of Szostak (U.S. Patent No. 5,631,146). The Action states that Gold does not teach anti-adenosine aptamers as in claims 38-39. The Action asserts, however, that Szostak teaches anti-adenosine aptamers, and that it would have been obvious to apply the anti-adenosine aptamers of Szostak to the target detection method of Gold. Appellant respectfully traverses this rejection.

As set forth above in section VII.C., the examiner failed to establish that Gold teaches all of the elements of the method recited in independent claim 29. Thus, regardless of whether Szostak teaches anti-adenosine aptamers, the Action still fails to establish that these references teach or suggest all of the limitations of independent claim 29. If an independent claim is nonobvious under 35 U.S.C. § 103(a), then any claim depending therefrom is nonobvious. MPEP § 2143.03. The examiner, therefore, failed to establish a *prima facie* case of obviousness against claims 38-39, which depend from claim 29. Appellant, therefore, respectfully requests that the Board overturn this rejection.

Respectfully submitted,



Travis M. Wohlers  
Reg. No. 57,423  
Attorney for Applicant

FULBRIGHT & JAWORSKI L.L.P.  
600 Congress Avenue, Suite 2400  
Austin, Texas 78701  
(512) 536-5654

Date: February 28, 2007

## CLAIMS APPENDIX

29. A method of transducing a conformational change in a signaling aptamer upon binding a ligand to an optical signal, the method comprising:

- (a) providing a signaling aptamer comprising a reporter molecule covalently coupled to an aptamer, wherein in an unbound state an optical signal produced by the reporter molecule is quenched by the aptamer's conformation and not by means of a separate quenching molecule covalently coupled to the signaling aptamer, relative to the optical signal produced by the reporter molecule when the aptamer undergoes a conformational change upon binding to its ligand;
- (b) contacting the signaling aptamer with the ligand under conditions whereby the signaling aptamer binds the ligand; and
- (c) detecting the optical signal produced by the reporter molecule as a result of the conformational change to the signaling aptamer upon binding the ligand.

30. The method of claim 29, further comprising the step of quantitating the amount of ligand bound to the signaling aptamer.

31. The method of claim 29, wherein the optical signal is selected from the group consisting of fluorescence, colorimetric intensity, anisotropy, polarization, lifetime, emission wavelength, and excitation wavelength.

32. The method of claim 29, wherein the covalent coupling of the reporter molecule to the signaling aptamer occurs during chemical synthesis, during transcription, or post-transcriptionally.

33. The method of claim 29, wherein the reporter molecule is a dye.

34. The method of claim 33, wherein the dye is a fluorescent dye.

35. The method of claim 34, wherein the fluorescent dye replaces a nucleic acid residue or is inserted between two nucleic acid residues of the signaling aptamer.

36. The method of claim 34, wherein the fluorescent dye is acridine or fluoresceine.

37. The method of claim 29, wherein the signaling aptamer comprises RNA, DNA, modified RNA, or modified DNA.

38. The method of claim 29, wherein the signaling aptamer is an anti-adenosine signaling aptamer.

39. The method of claim 38, wherein the anti-adenosine signaling aptamer is ATP-R-Ac13 or DFL7-8.

40. The method of claim 35, wherein the fluorescent dye replaces a nucleic acid residue adjacent to a functional nucleic acid residue of the aptamer or is inserted between the functional nucleic acid residue and the nucleic acid residue adjacent to the functional nucleic acid residue.

41. The method of claim 29, wherein the signaling aptamer is in solution.

42. The method of claim 29, wherein the signaling aptamer is immobilized on a solid support.

43. The method of claim 42, wherein the solid support is a chip.

**EVIDENCE APPENDIX**

None

**RELATED PROCEEDINGS APPENDIX**

None